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Understanding Low Testosterone:

Mechanisms, Symptoms, and Therapeutic Interventions

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Whitepaper

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Abstract

Testosterone is a key hormone that supports male physical, metabolic, sexual, and cognitive health. As levels decline, men may experience reductions in energy, libido, muscle mass, strength, mood stability, and mental clarity. Testosterone Replacement Therapy (TRT) aims to restore testosterone to normal physiological ranges, re-establishing androgen signaling and improving daily well-being. Clinical research, including large placebo-controlled trials, has demonstrated meaningful benefits of TRT across domains such as sexual function, body composition, vitality, mood, and metabolic health when used appropriately. Because testosterone influences multiple organ systems, safe and effective therapy requires structured medical oversight, laboratory monitoring, and individualized dosing. Fridays' clinician-led, at-home TRT program provides this guidance from initial testing through ongoing follow-ups, ensuring that hormone levels and symptom improvements are closely tracked. Overall, TRT represents a clinically validated approach for men with confirmed low testosterone, offering improvements in vitality, performance, and quality of life.

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1 Introduction

Testosterone is a central regulator of male physiology, influencing systems throughout the body. Beyond its well-known role in reproductive development, testosterone influences muscle mass, bone strength, metabolism, sexual function, mood, energy, and cognitive performance. When levels decline, whether due to aging, chronic stress, lifestyle factors, illness, or disruptions within the hypothalamic–pituitary–gonadal axis, men may experience wide-ranging changes in how they feel, look, and perform. Over time, this can lead to reduced vitality, diminished libido, decreased strength, increased fat mass, mood fluctuations, and impaired focus.

Testosterone Replacement Therapy (TRT) has emerged as a scientifically supported approach for restoring hormone levels and improving quality of life in men with confirmed deficiency. Clinical research, including large randomized trials, has explored TRT's benefits across domains such as energy, sexual function, body composition, mood, and cognitive well-being. This white paper reviews the physiology of testosterone, the causes and manifestations of low testosterone, and the current evidence supporting TRT.

2 Physiological Role of Testosterone

Testosterone has a significant impact on the development, function, and condition of multiple organs and systems throughout the body. Testosterone is an androgen and therefore plays an important role in male reproductive development and sexual function. However, it is also essential for maintaining muscle, bone, and metabolic health[1–3]. The hormone is also important in female physiology, though it is typically found at significantly lower levels. Here, we will focus on the role of testosterone in male physiology.

Testosterone is produced predominantly by Leydig cells in the testes in men, with small additional amounts coming from the adrenal glands. Its production is controlled by the hypothalamic–pituitary–gonadal axis[4]. The hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary to release luteinizing hormone (LH), which then acts on Leydig cells to convert cholesterol into testosterone[2,5].

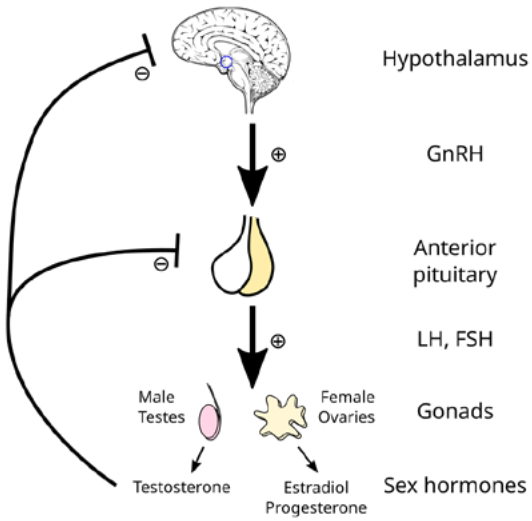

Figure 1. The Hypothalamic–Pituitary–Gonadal Axis. The hypothalamus releases GnRH, which signals the pituitary gland to secrete LH and FSH; these, in turn, stimulate the gonads (testes/ovaries) to produce sex hormones (testosterone, estrogen, progesterone) and gametes. The axis is tightly controlled by feedback from the gonadal hormones to both the hypothalamus and pituitary, enabling precise hormonal regulation for fertility and reproductive health. Adapted from Hypogonadism in exercising males: dysfunction or adaptive-regulatory adjustment? Hackney, A. C (2020). Used under Creative Commons License.

Once secreted, testosterone enters the bloodstream and is transported, typically bound to proteins[6]. In peripheral tissues, testosterone can be locally converted to dihydrotestosterone (DHT) by 5α-reductase or to estradiol by aromatase[7]. Together, these androgens and estrogens then act in target organs and feed back on the hypothalamus and pituitary to regulate further testosterone production[4]. Bioavailable testosterone is the fraction of testosterone in the blood that can actually act on tissues, and is comprised of testosterone loosely bound to albumin and free (unbound) hormone. Testosterone bound to sex hormone binding globulin (SHBG) cannot easily diffuse into most target cells and is biologically inactive[6,8,9].

Testosterone is essential for bone strength through both direct androgen receptor–mediated effects and indirect conversion to estradiol, working across the lifespan to build peak bone mass during growth and maintain bone density and architecture in adulthood[10,11]. Testosterone is also critical for muscle strength. It promotes muscle fiber growth, supports protein synthesis, and improves neuromuscular function, which together increase muscle mass and the capacity to generate force[12,13]. Furthermore, testosterone activity impacts metabolism by regulating carbohydrate, fat, and protein pathways across multiple tissues, thereby influencing body composition, insulin sensitivity, energy expenditure, and metabolic disease risk[14].

In addition to strength, energy, and muscle building, testosterone impacts libido (sexual desire) through central nervous system pathways and peripheral mechanisms that together regulate motivation for sexual activity, sensitivity to sexual stimuli, and physiological arousal[15]. There is also evidence that testosterone has a significant impact on mood and cognition: men with low levels show higher rates of depressive symptoms, fatigue, irritability, and emotional lability[16]. Low testosterone is frequently associated with cognitive symptoms such as brain fog, reduced concentration, slowed thinking, and indecisiveness, which themselves worsen mood, well-being, and quality of life[17,18].

3 Age-Related Decline

Testosterone concentrations in males exhibit a characteristic, non-linear pattern across the lifespan. Levels are very low during childhood, and rise during two critical developmental periods: minipuberty in infancy and the onset of puberty in adolescence. They reach their peak in the late teenage years to early twenties. Thereafter, testosterone gradually declines. The age-related decline in testosterone from around 30 years of age is known as andropause, and is related to a range of physiological and psychological symptoms.

Most studies report a gradual reduction in total testosterone levels with increasing age, particularly after age 40 or 50, with more pronounced decreases in older men. Total testosterone falls by an average of 1.6% per year, while bioavailable testosterone declines more sharply, often at rates of 2-3% per year[19,20]. Age-related changes in free testosterone are larger because SHBG levels also increase with age, increasing the amount of bound hormone[20]. Low bioavailable testosterone is more closely associated with symptoms of andropause and functional changes. The rate and pattern of testosterone decline vary between populations and are influenced by factors such as comorbidities, obesity, and cardiovascular disease. Healthy aging men may show more stable levels, and genetic factors appear less influential than lifestyle and health status[21,22].

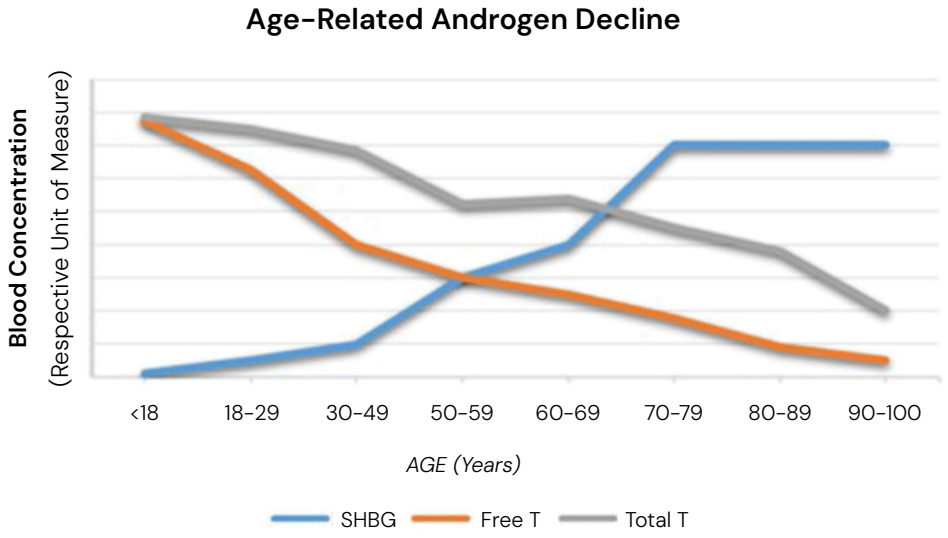

Figure 2. Age-Related Decline in Testosterone in Men. Decreases in total testosterone levels and free (bioavailable) testosterone are associated with increases in testosterone-binding SHBG. Adapted from Hypogonadism in exercising males: dysfunction or adaptive-regulatory adjustment? Hackney, A. C (2020). Used under Creative Commons License.

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4 Symptoms of Low Testosterone

Alongside age-related declines, low testosterone can be caused by a variety of factors, including obesity, some genetic conditions, damage to the testicles, infections, type 2 diabetes, chronic liver or kidney disease, excess alcohol and drug use, and significant psychological stress[23]. Low testosterone is associated with a broad but nonspecific set of symptoms. Individuals vary considerably in the type and severity of symptoms they experience, and many manifestations have additional or alternative causes, such as obesity, chronic medical conditions, or medication effects. Nonetheless, clinical and epidemiologic studies describe several recurring symptom domains.

4.1. Body Composition and Physical Performance

Age-related testosterone decline is associated with loss of lean muscle mass and strength, reduced exercise tolerance, and an increase in total and central (abdominal or visceral) adiposity. Declining bone mineral density can lead to gradual height loss, vertebral changes, and an elevated risk of fractures[11,24].

4.2. Energy, Mood, and Cognition

Fatigue, low energy, and reduced stamina are frequently reported[25]. Mood-related symptoms may include low mood, irritability, diminished motivation, and reduced self-confidence; some individuals develop mild depressive symptoms. Cognitive complaints often encompass "brain fog," decreased concentration, slowed information processing, and mild memory difficulties[26].

4.3. Sexual Function

Diminished sexual desire and reduced frequency of sexual thoughts are common. Men may experience fewer morning or spontaneous erections, erectile dysfunction, reduced ejaculate volume, and, in some cases, decreased fertility[27,28].

4.4. Other Symptoms

More pronounced testosterone deficiency can produce vasomotor symptoms such as hot flushes or night sweats. Sleep disturbance, including insomnia, nonrestorative sleep, or excessive sleepiness, is also reported. Additional changes may include reduced beard or body-hair growth, drier or thinner skin, mild anemia, and a worsened cardiometabolic profile characterized by increased visceral fat, insulin resistance, and adverse lipid changes[29].

5 Testosterone Treatments and TRT

Testosterone replacement therapy (TRT) restores circulating testosterone to physiological levels, allowing it to exert its usual androgenic and estrogenic effects in target tissues. The mechanism is the same as endogenous testosterone, just with an external source. Exogenous testosterone increases serum total and free testosterone, and higher circulating testosterone re-establishes androgen signaling in tissues that had been under-stimulated.

TRT is only designed to restore testosterone to normal levels; pushing levels into a supraphysiologic range adds relatively little clinical benefit but markedly increases adverse effects and system stress. High dosing produces much stronger negative feedback on GnRH, LH, and follicle-stimulating hormone (FSH), driving profound reductions in intratesticular testosterone, severe suppression of spermatogenesis, testicular atrophy, and often prolonged infertility[30,31].

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6 Evidence for TRT in Key Domains

Much of the clinical evidence for the impact of testosterone comes from studies of hypogonadism. Hypogonadism is a clinical syndrome characterized by symptoms and signs of androgen or sperm deficiency and its diagnosis normally requires biochemical evidence of testosterone deficiency due to impaired function of the hypothalamic–pituitary–testicular axis. However, clinical trials have also investigated the use of TRT to support men with age-related declines in testosterone, as well as men with symptoms of low androgen levels.

Two large clinical research projects, the T-Trials and the TRAVERSE (TheRapy for Assessment of long-term Vascular events and Efficacy ResponSE in hypogonadal men), represent an important step in research into the impacts of TRT. The T-Trials encompassed seven placebo-controlled, double-blind trials involving 788 men with low testosterone[32], while TRAVERSE was a multicentre randomized, placebo-controlled, double-blind trial of testosterone therapy in 5,246 men 45 to 80 years of age. Participants in TRAVERSE also recruited men with a high risk of cardiovascular disease to assess the safety of TRT in these patients.

Here, we will outline evidence from these trials and elsewhere on the impact of TRT on key domains related to testosterone function.

6.1. Muscle Mass, Strength, and Body Composition

The T-Trials and TRAVERSE showed that testosterone therapy also influences muscle mass, strength, and body composition, with consistently documented increases in lean body mass (1.5–5 kg) and reductions in fat mass (1–4 kg) over the course of 2-3 years. Improvements were seen in leg press, chest press, and stair-climbing power. Functional gains, including increased walking distance or better self-reported mobility, were also observed[33].

These improvements were also demonstrated in the TEAAM trial, which recruited men with low-normal levels of testosterone, and in the 4DM trial, which investigated the use of TRT as a way to prevent or reverse type 2 diabetes[34,35]. Meta-analyses, which combine the data from multiple trials, consistently show that TRT increases lean mass and improves strength and body composition, with the most significant gains in men who start with clearly low testosterone[36,37].

6.2. Libido and Sexual Performance

The most consistent positive effects of testosterone therapy observed across trials were in libido and sexual performance. The Sexual Function T-Trial and meta-analyses demonstrate consistent, statistically significant improvements in sexual desire, libido, sexual activity, and overall sexual satisfaction compared to placebo[38]. These improvements included more frequent sexual thoughts and behaviors. Effects on erectile dysfunction were also reported, and testosterone is now often used as an adjunct to conventional erectile dysfunction medication such as PDE5 inhibitors.

The TRAVERSE trial also found that testosterone therapy improved sexual activity and libido among the subgroup of men with self-reported low libido[39]. The T4DM trial, which investigated the use of TRT as a way to prevent or reverse type 2 diabetes, also found similarly improved erectile dysfunction, sexual desire, and overall sexual satisfaction[40].

6.3. Energy, Mood, and Cognitive Function

Testosterone therapy shows meaningful effects on energy, mood, and cognitive function. In trials involving men with low testosterone levels, such as the T-Trials and TRAVERSE, participants experienced improvements in vitality, including better self-reported energy. TRT also improved mood and reduced depressive symptoms, as measured by the Patient Health Questionnaire-9 and affect scales[41,42]. In contrast, studies that included men with normal testosterone, such as TEAAM, found no significant improvements in energy[43].

Elsewhere, epidemiologic data have linked lower endogenous testosterone or bioavailable testosterone with greater risk of cognitive decline and dementia, and basic studies show that androgens can have neuroprotective effects. Small trials in older men with low testosterone or cognitive complaints reported improvements in verbal or spatial memory and global cognition after several months of testosterone supplementation[44,45].

6.4. Metabolic Health

TRT has a positive impact on metabolic health, especially in early or pre-diabetic states. In the T-Trials, testosterone reduced fasting insulin and improved insulin resistance[35]. The T4DM trial showed that testosterone, when used alongside a structured lifestyle program, decreased fasting glucose and significantly lowered the progression to type 2 diabetes[40]. Notably, these benefits were most evident in high-risk men with early metabolic dysfunction.

The loss of visceral body fat associated with TRT can also have profound impacts on metabolic health, including improvements in lipid parameters. Visceral fat loss decreases very low-density lipid (VLDL) and triglyceride production by reducing portal FFA delivery to the liver, as well as reducing inflammatory adipokine and cytokine output[46].

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7 Other Treatments for Low Testosterone

7.1. Enclomiphene

Enclomiphene is an oral selective estrogen receptor modulator (SERM) developed as a targeted treatment for men with hypogonadism and low testosterone. It acts mainly at the hypothalamus and pituitary to increase endogenous testosterone production rather than supplying testosterone directly.

Mechanistically, enclomiphene blocks estrogen receptors in the hypothalamus and pituitary, reducing estrogen's negative feedback on GnRH, LH, and FSH. This increases GnRH release and raises LH and FSH, which in turn stimulate the testes to produce more testosterone and support spermatogenesis. As a result, serum testosterone typically rises into the normal range while LH and FSH remain normal or elevated, and testicular size and sperm production are generally preserved[47].

Clinically, this makes enclomiphene conceptually attractive for younger men with secondary hypogonadism who want to raise testosterone but maintain or improve fertility, in contrast to traditional TRT, which often suppresses LH/FSH and intratesticular testosterone and can markedly reduce sperm counts.

7.2. Gonadorelin

Gonadorelin is a synthetic form of GnRH, which acts as a GnRH receptor agonist and is biologically identical to endogenous GnRH. Gonadorelin stimulates the pituitary gland to release LH and follicle-stimulating hormone FSH, which then act on the testes (in men) or ovaries (in women) to regulate sex hormone production, including testosterone.

If low testosterone is due to insufficient hypothalamic GnRH output, gonadorelin can mimic normal GnRH pulses, increase LH and FSH, and thereby raise endogenous testosterone while also supporting spermatogenesis. As such, Gonadorelin treats the upstream defect and can normalize both T and fertility without shutting the axis down, unlike conventional TRT[48].

8 Safety, Monitoring, and Clinical Oversight

TRT affects multiple systems (hematopoietic, cardiovascular, prostate, metabolic, reproductive), and adverse effects like polycythemia, edema, sleep apnea, and thromboembolism are dose- and duration-dependent. Ongoing medical supervision allows dose titration to keep levels within the physiological range and ensures that the original treatment goals are actually being met. Supervision also coordinates shared decisions about when to pause or stop therapy if benefits plateau or if new comorbidities emerge.

9 Fridays' Testosterone Protocol

Fridays' Testosterone Replacement Therapy (TRT) program is structured to combine evidence-based medicine with the convenience of at-home care. After completing sign-up, patients receive an order for baseline laboratory testing directly in their secure patient portal. These labs are completed before the first consultation so that the clinician can interpret results in the context of symptoms and medical history.

Additional lab work is typically scheduled at 1 month, 3 months, and then every three months until your levels are stable. Once stability is reached, regular lab checks continue, typically annually, though clinicians may recommend more frequent testing if needed.

Friday's offers testosterone in oral and injectable forms, each offering different advantages in convenience and stability. Intramuscular injections are reliable and cost-effective but require needles, while oral testosterone provides a familiar pill-based route. The best delivery method depends on lifestyle, preferences, cost, and how tightly hormone levels need to be managed. Fridays' at-home program enhances convenience without sacrificing safety.

10 Side Effects and Risk Mitigation

Side effects and risks with TRT are largely predictable and, in most men, manageable if therapy is properly dosed and monitored. Common side effects may include acne, oily skin, increased body hair, hair thinning, mood fluctuations, elevated estradiol levels, or testicular atrophy. Because TRT can suppress LH and FSH, it may also reduce sperm production and negatively impact fertility[49].

More significant risks can include increased red blood cell count (raising hematocrit), changes in blood pressure, sleep apnea exacerbation, or prostate-related symptoms in susceptible individuals. These reactions are typically manageable when identified early.

Fridays mitigates these risks through structured clinical oversight and regular lab monitoring, as outlined above. This approach ensures that testosterone levels remain within a healthy physiological range and safety markers are closely tracked.

11 Conclusion

Testosterone plays a central role in male physical, metabolic, sexual, and cognitive health, and its gradual decline can meaningfully impact daily performance and overall well-being. A substantial body of clinical evidence demonstrates that restoring testosterone to physiological levels can improve energy, libido, mood, cognition, muscle mass, and body composition in men with documented deficiency. These benefits are most reliable when therapy is medically supervised and individualized to each patient's symptoms, goals, and underlying health status. Like any hormonal treatment, TRT requires careful monitoring to remain safe. Structured oversight, routine laboratory evaluations, and evidence-based dosing minimize risks.

By combining convenient testing, clinician-guided treatment, and ongoing monitoring, Fridays ensure that men can access high-quality hormone optimization without sacrificing safety. The goal is to restore balance, supporting vitality, performance, and day-to-day well-being. For men experiencing the effects of low testosterone, medically guided TRT offers a safe, effective, and patient-centered path toward feeling stronger, clearer, and more like themselves again.


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7 References

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